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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/934,060	08/21/2001	Anthony Louis Devico	4115-144 CIP	8085

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INTELLECTUAL PROPERTY / TECHNOLOGY LAW
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EXAMINER	
WINKLER, ULRIKE	
ART UNIT	**PAPER NUMBER**
1648	

DATE MAILED: 05/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/934,060	DEVICO ET AL.	
	Examiner	Art Unit	
	Ulrike Winkler	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 February 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,8-16,36-39 and 41-57* is/are pending in the application.

4a) Of the above claim(s) *36-39,41-54,56 and 57* is/are withdrawn from consideration.

5)☒ Claim(s) *2-4 and 55* is/are allowed.

6)☒ Claim(s) *1, 8-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The Amendment filed February 13, 2004 in response to the Office Action of November 13, 2003 is acknowledged and has been entered. Claims 5-7, 17-35, 40, 53-54 have been cancelled. Claims 1-4, 8-16 and 55 are pending and are currently being examined.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Claim Rejections - 35 USC § 102

The rejection of claims 1, 8 and 11 under 35 U.S.C. 102(e) as being anticipated by Young et al. (U.S. Pat. No. 6,060,316) **is withdrawn** in view of Applicant's amendment to the claims.

Claim Rejections - 35 USC § 103

The rejection of claims 1, 5-16 rejected under 35 U.S.C. 103(a) as being unpatentable over Young et al (U.S. Pat. No. 6,060,316) and DeVico et al. (U.S. Pat. No. 5,843,454, IDS) or DeVico et al. (U.S. Pat. No. 5,518,723, IDS) in view of Stratagene Catalog (1997/1998) is **withdrawn** in view of Applicant's amendment to the claims.

Double Patenting

The rejection of claims 1, 5-11 and 15, 16 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 3 of U.S. Patent No. 5,518,723 in view of Young et al (U.S. Pat. No. 6,060,316) **is withdrawn** in view of Applicant's amendment to the claims.

The rejection of claims 1, 5-11 and 15, 16 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 5,843,454 in view of Young et al. (U.S. Pat. No. 6,06,316) **is withdrawn** in view of Applicants amendment to the claims.

Claim Objections

The objection of claims 2-4 and 55 **is withdrawn** in view of Applicant's amendment to the claims.

New Rejection in view of Applicant's Amendments to the Claims:

Claim Rejections - 35 USC § 103

The rejection of claims 1, 5-16 rejected under 35 U.S.C. 103(a) as being unpatentable over Young et al (U.S. Pat. No. 6,060,316) and DeVico et al. (U.S. Pat. No. 5,843,454, IDS) or DeVico et al. (U.S. Pat. No. 5,518,723, IDS) in view of Freed et al. (Journal of Virology, 1989) and further in view of Stratagene Catalog (1997/1998).

Applicant's arguments have been fully considered but fail to persuade. Applicant's argument are (1) that none of the references suggest using a mutated furin cleavage site on the C-terminus of the gp120 portion of the fusion protein and (2) that the Office has not given any weight considering the unexpected results using the specific compounds disclosed in the instant specification.

> MPEP 716.02 "A greater than expected result is an evidentiary factor pertinent to the legal conclusion of obviousness ... of the claims at issue." *In re Corkill*, 711 F.2d

> 1496, 226 USPQ 1005 (Fed. Cir. 1985). *In Corkhill*, the claimed combination showed an additive result when a diminished result would have been expected. This result was persuasive of nonobviousness even though the result was equal to that of one component alone. Evidence of a greater than expected result may also be shown by demonstrating an effect which is greater than the sum of each of the effects taken separately (i.e., demonstrating "synergism"). *Merck & Co. Inc. v. Biocraft Laboratories Inc.*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989). However, a greater than additive effect is not necessarily sufficient to overcome a *prima facie* case of obviousness because such an effect can either be expected or unexpected. Applicants must further show that the results were greater than those which would have been expected from the prior art to an unobvious extent, and that the results are of a significant, practical advantage.

Applicants arguments are that the prevention of the cleavage of the single chain complex between gp120 and CD4 is an unexpected result in that is stabilizes the complex. This is not found persuasive because the prior art has shown that in order to maintain gp160 as a single chain expression product requires the mutation of Arg→ Thr at the gp120/gp41 junction which happens to be the furin cleavage site (see Freed et al., Journal of Virology, Table 2).

The instant invention is directed to a chimeric polypeptide comprising a viral coat polypeptide from a retrovirus and a viral receptor. The sequences are linked by an amino acid spacer allowing the receptor and ligand to bind each other. The chimeric polypeptide can comprise a tag.

Young et al. teach the production of a soluble viral receptor and ligand fusion moieties which can be directly bonded together or through a linking moiety. Where one or both of the moieties are polypeptides, a peptide bond or peptide linker is preferred, thereby obtaining a "fusion protein" of the two moieties which can be expressed by a single nucleic acid construct in series. The two moieties can alternatively be linked directly or indirectly other than via a peptide bond or peptide linker, thereby obtaining a "conjugate" (see column 9, lines 40-50). If a linking

moiety is employed to link the two moieties. The linker can preferably be a flexible linker and sufficient in length to separate the moieties in space, thereby not restricting the ability of the soluble viral receptor-ligand fusion molecule to bind independently and maintain the proper conformation. Where both moieties are polypeptides, the linker moiety will generally be a peptide, polypeptide, or a "pseudopeptide" (see column 9 line 66 to column 10 line 5). The reference indicates that the viral surface protein (envelope) is generally the viral protein that binds the cell and activated viral entry (see column 8, lines 48-52), and the cellular receptor for retroviruses is CD4 (see column 8, lines 58-61). The reference does not teach using the composition in a pharmaceutically acceptable carrier.

DeVico et al. disclose in both patents a CD4-gp120 complex that has been covalently linked using a reactive spacer molecule. The reference teaches using the complex as a vaccine. The reference teaches that the interaction between the virus coat protein and the virus receptor exposes cryptic epitopes that are not present with the viral coat protein or the CD4 receptor alone (see table 1). Gp120 and CD4 have an affinity for one another and spontaneously form a complex when placed in a solution together. The reference does not teach using an amino acid spacer in the production of the antigenic complex.

Freed et al. teaches that a mutation at the C terminal region of gp120 from Arg→ Thr at the gp120/gp41 junction results in a single chain expression product that is not cleaved by endogenous cellular proteases (see figure 3). The mutation site happens to be within the furin cleavage site.

Stratagene Catalog discloses the use of protein expression vectors using an affinity tag for the purpose of easily purifying the desired protein. The reference does not disclose the expression of a virus coat/virus receptor fusion protein.

It is well established in the art that endogenous cellular proteases, which includes furin, cleaves the gp160 into the respective subunits gp120 and gp41. It would have been obvious to one of ordinary skill in the art to at the time the invention was made to either add a mutation to the furin cleavage site of gp120 or to delete the site entirely in order to produce a single chain amino acid sequence that will not be subject to digestion by endogenous cellular proteases. It would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize a chimera for the production of the gp120-CD4 complex. The chimera as taught by Young et al. requires the single process step utilizing affinity purification after the expression of the fusion protein. One having ordinary skill in the art would have been motivated to make a gp120-CD4 chimera to achieve the conformational complex as taught by DeVico et al. which would have the advantage of requiring less process steps in order to achieve the same function. The prior art requires purifying the CD4 and the gp120 proteins separately allowing them to interact and then chemically cross linking followed by the removal of the excess cross linker. One having ordinary skill in the art would have a high expectation of success when expressing the complex as a single polypeptide. The addition of amino acid linkers would have been obvious to the ordinary artisan in order to alleviate potential folding constraints in the fusion protein as suggested by Young et al. (see column 10, lines 1-5). The use of an expression or affinity tag for the purpose is well established in the art as shown by the availability of such tools using commercial vendors (Stratagene Catalog). If the addition of the affinity tag produces an

unexpected result, applicant will need to point out what the unexpected result are. Therefore, the instant invention is obvious over Young et al. and DeVico et al. in view of in view of Freed et al. (Journal of Virology, 1989) and further in view of Stratagene Catalog.

Double Patenting

Claims 1, 5-11 and 15, 16 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 3 of U.S. Patent No. 5,518,723 in view of Young et al (U.S. Pat. No. 6,060,316) and Freed et al. (Journal of Virology, 1989).

Applicant's argument to the prior double patenting rejection is that the Office is not at liberty to resort to the text of the different specifications for additional facts to support obvious double patenting rejection.

> MPEP 804 : The specification can always be used as a dictionary to learn the meaning of a term in the patent claim. *In re Boylan*, 392 F.2d 1017, 157 USPQ 370 (CCPA 1968). Further, those portions of the specification which provide support for the patent claims may also be examined and considered when addressing the issue of whether a claim in the application defines an obvious variation of an invention claimed in the patent. *In re Vogel*, 422 F.2d 438, 441-42, 164 USPQ 619, 622 (CCPA 1970). The court in Vogel recognized "that it is most difficult, if not meaningless, to try to say what is or is not an obvious variation of a claim," but that one can judge whether or not the invention claimed in an application is an obvious variation of an embodiment disclosed in the patent which provides support for the patent claim. According to the court, one must first "determine how much of the patent disclosure pertains to the invention claimed in the patent" because only "[t]his portion of the specification supports the patent claims and may be considered." The court pointed out that "this use of the disclosure is not in contravention of the cases forbidding its use as prior art, nor is it applying the patent as a reference under 35 U.S.C. 103, since only the disclosure of the invention claimed in the patent may be examined."

Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant invention is directed to a chimeric polypeptide comprising a viral coat polypeptide sequence and a viral receptor. The sequences are linked by an amino acid chain that function to allow formation of an interacting complex between the virus coat polypeptide sequence and receptor polypeptide sequence (specification, page 14, line 23-31). The U.S. Patent No. 5,518,723 discloses CD4-gp120 (claim 1) which is drawn to an immunogenic complex comprising gp120 covalently bonded to CD4 so that cryptic epitopes are exposed. The patent includes the complex in a pharmaceutically acceptable carrier. A peptide bond is a covalent bond because it involves the sharing of electrons. Young et al. teach the production of a chimera between a viral coat protein (Env) and cell surface receptor (CD4) for the production of a fusion protein complex. The soluble viral receptor and ligand fusion moieties of the soluble viral receptor-ligand fusion molecule can be directly bonded together (like the complex found in the DeVico patent) or through a linking moiety. Where one or both of the moieties are polypeptides, a peptide bond or peptide linker is preferred, thereby obtaining a fusion protein of two moieties which can be expressed by a single nucleic acid construct (see Young et al. column 9, lines 40-50). It is well established in the art that endogenous proteases cleave the single chain product gp160 into gp120 and gp41. Freed et al. teaches that a mutation at the C terminal region of gp120 from Arg→ Thr at the gp120/gp41 junction results in a single chain expression product that is not cleaved by endogenous cellular proteases (see figure 3).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize a chimera for the production of the gp120-CD4 complex as taught by DeVico et al. The gp120 and CD4 molecules have a natural affinity for another and form the

complex spontaneously. One ordinary skill in the art would have been motivated to make a gp120-CD4 chimera to reduce the process steps in order to achieve the same function. The chimera as taught by Young et al. requires the single process step. One of ordinary skill in the art would have been motivated to remove the endogenous protease cleavage site from the single chaim product in order to maintain the integrity of the product in the cell. One having ordinary skill in the art would have a high expectation of success when expressing the complex as a single polypeptide. The addition of amino acid linkers would have been obvious to the ordinary artisan in order to alleviate potential folding constraints in the chimera as suggested by Young et al.

The rejection of claims 1, 5-11 and 15, 16 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 5,843,454 in view of Young et al. (U.S. Pat. No. 6,06,316) and Freed et al. (Journal of Virology, 1989).

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> considered." The court pointed out that "this use of the disclosure is not in contravention of the cases forbidding its use as prior art, nor is it applying the patent as a reference under 35 U.S.C. 103, since only the disclosure of the invention claimed in the patent may be examined."

Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant invention is directed to a chimeric polypeptide comprising a viral coat polypeptide sequence and a viral receptor. The sequences are linked by an amino acid chain that function to allow formation of an interacting complex between the virus coat polypeptide sequence and receptor polypeptide sequence (specification, page 14, line 23-31). The U.S. Patent No. 5,843,454 discloses CD4-gp120 (claim 1) is drawn to an immunogenic complex comprising gp120 covalently bonded to CD4. The patent includes the complex in a pharmaceutically acceptable carrier. A peptide bond is a covalent bond because it involves the sharing of electrons. . Young et al. teach the production of a chimera between a viral coat protein (Env) and cell surface receptor (CD4) for the production of a fusion protein complex. The soluble viral receptor and ligand fusion moieties of the soluble viral receptor-ligand fusion molecule can be directly bonded together (like the complex found in the DeVico patent) or through a linking moiety. Where one or both of the moieties are polypeptides, a peptide bond or peptide linker is preferred, thereby obtaining a fusion protein of two moieties which can be expressed by a single nucleic acid construct (see Young et al. column 9, lines 40-50). It is well established in the art that endogenous proteases cleave the single chain product gp160 into gp120 and gp41. Freed et al. teaches that a mutation at the C terminal region of gp120 from Arg→ Thr at the gp120/gp41 junction results in a single chain expression product that is not cleaved by endogenous cellular proteases (see figure 3).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize a chimera for the production of the gp120-CD4 complex as taught by DeVico et al. The gp120 and CD4 molecules have a natural affinity for another and form the complex spontaneously. One ordinary skill in the art would have been motivated to make a gp120-CD4 chimera to reduce the process steps in order to achieve the same function. The chimera as taught by Young et al. requires the single process step. One of ordinary skill in the art would have been motivated to remove the endogenous protease cleavage site from the single chaim product in order to maintain the integrity of the product in the cell. One having ordinary skill in the art would have a high expectation of success when expressing the complex as a single polypeptide. The addition of amino acid linkers would have been obvious to the ordinary artisan in order to alleviate potential folding constraints in the chimera as suggested by Young et al.

Conclusion

Claims 1 and 8-16 are rejected.

Claims 2-4 and 55 are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Papers related this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG (November 15, 1989). The Group 1600 Official Fax number is: (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Tech Center representative whose telephone number is (571)-272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ulrike Winkler, Ph.D. whose telephone number is 571-272-0912. The examiner can normally be reached M-F, 8:30 am - 5 pm. The examiner can also be reached via email [ulrike.winkler@uspto.gov].

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached at 571-272-0902.

ULRIKE WINKLER, PHD.
PATENT EXAMINER 5/14/04